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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/827,255	04/05/2001	Jeffrey Tze Fei Wong	1441830001336	4343

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	20

DATE MAILED: 12/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

F6

Office Action Summary	Application No.	Applicant(s)	
	09/827,255	WONG ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cov r she t with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed August 6, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed February 6, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 5, 2003 has been entered.

Response to Arguments

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for liposome composition having PC:Chol:PS ration of 11:4:0.025encompassing doxorubicin as the therapeutic agent coupled to aplpha1 acid-glycoprotein by avidin-biotin bridges, does not reasonably provide enablement for any liposome composition for the targeted

delivery of a therapeutic agent to a tissue expressing asialoglycoprotein receptors as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, and is repeated for the same reasons of record as set forth in the Office action mailed August 6, 2002.

Applicants response indicates their understanding that the instant rejection was maintained due to the presence of the term "therapeutic" in claims 1-7 and 9. Applicants believe that the present amendment which eliminates "therapeutic" in favor of "active agent" obviates this rejection.

This amendment and argument is considered partly convincing. The amendment obviates the rejection of record against the compositions of claims 1-6 and 9, but is maintained against the method of claim 7, because said method encompasses treatments that are not considered enabled for reasons of record. Since applicants has not presented any arguments directed to this, the rejection is maintained.

Claim Objections

Claim 3 is objected to because of the following informalities: there is no article preceding the term "cDNA". Inserting "a" just prior to said term would be remedial. Appropriate correction is required.

Claim 4 is objected to because the article "a" previous to "cytotoxic drugs" is singular, and does not agree with the plural term "drugs" to which it refers. Replacement with "an" would

Claim 5 is objected to because of the following informalities: The term "amphiphatic" is unknown in the art, and it appears that this is a misspelling of "amphipathic". Appropriate correction is required.

Claims 6 and 9 are objected to because of the following informalities: The term "avidinbiotin" as spelled in claim 6 is not recognized in the art. If applicants intend to claim an avidin-biotin linkage, which is an art recognized term, appropriate spelling correction is required. Furthermore, in claim 9, it appears there should be a space after the first two letters of "anavadin-biotin linkage". Claim 9 also recites an "asialoglycoproteing" which appears to be a misspelling of asialoglycoprotein. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants' claims recite "an effective amount of the agent encapsulated in a liposome..." but have not indicated what the amount must be effective for, rendering the metes and bounds of the claim indefinite.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim uses Markush-type language in referring to "the agent selected from the group consisting of a cytotoxic drugs, a protein." From M.P.E.P. § 2173.05(h),

> "When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, if "wherein is a material selected from the group consisting of A, B, C and D" is a proper limitation, then "wherein R is A, B, C or D" shall also be considered proper.

The Markush group elements of claim 4 recite neither "and" nor "or", and it is thus unclear whether the two entities are claimed as a conjugate or as separate elements. Insertion of the word "and" between the two elements of the Markush group would obviate this rejection, provided that applicants desire to claim these as separate elements.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written

description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The invention of claim 3 is drawn to the composition of claim 2, wherein the polynulceotide is cDNA encoding a protein, a ribozyme and antisense DNA. The specification does not describe any such cDNA. Furthermore, while it may be possible to make such a cDNA comprising all three of these elements, neither the prior art nor applicants specification discloses either prophetically or by way of example any use for the claimed composition. Thus, applicants are not considered to be in possession of such a molecule.

If it is applicants' intention to claim these cDNA-encoded elements in the alternative, then replacement of the word "and" with "or" would obviate this rejection.

Claim Rejections - 35 USC § 103

Claims 1-7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allen et al., Perez-Solar et al., Pratt et al., Martin, Hortobagyi, Menezes et al., Neitchev et al., and Mayer et al., all of record.

Allen et al., is relied upon to teach targeted liposomal drug delivery: "One way to increase the therapeutic index of drugs such as anticancer drugs, which have low therapeutic indices would be by specifically targeting the drugs to the diseased cells." See abstract. They specifically teach doxorubicin-loaded liposomes, and Ab-biotin coupling mechanisms on page 120 for example. They teach that any ligands may be coupled to such liposomes. They do not specifically teach desialyated glycoprotein-α-1.

Hortobagyi et al. is relied upon to teach anthracyclines as drugs used in treatments of cancer. They teach liposomal encapsulation of doxorubicin but do not teach coupling to desialyated glycoprotein-α-1.

Martin is further relied upon to teach liposomal doxorubicin administration compositions for the treatment of cancer but do not teach coupling to desialyated glycoprotein-α-1.

Menezes et al., is relied upon to teach Bcl-2 antisense/dox compositions but do not teach coupling to desialyated glycoprotein-α-1.

Pratt et al. and Mayer et al. are both relied upon to teach the advantage of using liposomal anthracycline formulations "is the potential for reductions in observed dose-limiting cardiotoxicity relative to either daunorubicin or doxorubicin as free drug" (See Pratt et al. page 47) and that doxorubicin could be administered at >2-fold higher doses when entrapped in liposomes" (Mayer et al., page 105, lines 6 and 7).

Perez-Soler et al. is relied upon to teach "the potential advantages of liposome-encapsulated doxorubicin are a reduced cardiotoxicity as a results of lower cardiac drug levels and an increased activity against rumors that infiltrate the liver and spleen. Different investigators showed a few years ago that liposome entrapment of doxorubicin results in a reduction of drug-related cardiotoxicity in animals." See page 4260.

Park et al. is relied upon to teach that the "the ASGPR [asialoglycoprotein receptor system] is also considered as a novel approach for targeted gene or drug delivery in to liver cells." See page 304. They are thus relied upon to teach the motivation of using agents which bind the asialoglycoprotein receptor, which encompasses glycoprotein agents, for targeted drug deliver to the liver.

Neitchev et al., is relied upon to teach liposomes conjugated to α-1 glycoprotein. They do not specifically teach use of such liposomes to targeted delivery of therapeutic compositions for the liver, although liposomes are generally well known in the art for use in delivery of pharmaceutical compositions and glycoproteins associated with the asialoglycoprotein receptor.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to make a composition for targeted diver of a therapeutic agent to a tissue, such as liver tissue, expressing asialoglycoprotein receptors comprising an agent such as a cytotoxic drug such as theanthracyclines (such as doxorubicin, daunorubicin or vincristine, etc.) or an antisense agent (such as that taught by Menezes et al.) encapsulated in a liposome coupled to a targeting agent to the asialoglycoprotein receptors such as the α-1 glycoprotein taught by Neitchev et al., since formation of anthracycline-liposome formulations was well-known in the art for the treatment of cancers and more specifically, targeting asialoglycoprotein receptors was well-known in the art for targeting liver cells. It would have further been obvious to couple the glycoprotein-α-1 by well-known means to the liposome as taught by Allen et al. It would further have been obvious to use such formulations for methods of targeting the composition to cancerous liver tissues for the benefits taught by Pratt et al., Mayer et al., and Perez-Soler et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to make anthracycline containing liposomes for treatments of various cancers as taught by Hortobagyi and Martin and having any type of targeting agent coupled to the liposome (Allen et al.). One of ordinary skill in the art would have been motivated to administer such compositions for the benefits taught by Mayer et al., Pratt et al., and Perez-Soler et al. Park et al.

further taught the specific motivation for use of asialoglycoprotein receptors for drug delivery to liver cells and liposomes specifically containing α-acid glycoprotein as taught by Neitchev et al.

One of ordinary skill in the art would have had an expectation of success to design composition for the targeted delivery of a known therapeutic agent to a tissue, such as liver tissue, expressing asialoglycoprotein receptors since (1) anthracycline/liposome compositions were well-known in the art as taught above, (2) Perez-Soler et al. taught the accumulation of such compositions in liver cells in the absence of specific targeting (3) composition such as α-1 acid glycoprotein were known in the art as coupled to liposomes and specific drug targeting to asialoglycoprotein receptors was also known in the art, as were (4) many coupling mechanisms known in the art for specific conjugation of targeting agents to liposomes (Allen et al.). Although one of ordinary skill in the art would not have had an expectation of success for any possible therapeutic agent to be delivered for treatment effects of any disease in whole organisms, one of ordinary skill would have had the expectation that known anthracycline/liposomes coupled to glycoprotein α-1 would have had an expectation for having some success in targeting the liver cells for therapeutic purposes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD

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